REMARKS

Claims 14-16 have been amended for clarification. The scope of these claims remains the same. New claims 20-22 are supported in Example 3 of the specification and on page 1, fourth line from the bottom. No new matter has been added and entry of the amendment is respectfully requested.

The previous rejections of claims 1-13 under 35 U.S.C. § 102 and 35 U.S.C. § 103 and for obviousness-type double-patenting over U.S. patent 4,891,319 and provisionally over claims 7 and 24-28 of copending application 08/875,796 are obviated in view of the cancellation of these claims.

The Invention

The invention is based on the advantageous combination of trehalose with freeze-drying to prepare stabile compositions of Factor VIII, specifically. Proteins vary in terms of their ability to exist as stabile compositions and in their behavior on freeze-drying, since the proteins differ in three-dimensional conformation, the nature of their active sites, and a multiplicity of other factors that determine the speed and completeness of denaturation as water is removed. As noted in Roser I, of record herein, a great deal of water is hydrogen bonded to biological molecules (page 47, left-hand column) and as this is removed by freeze-drying, unless the molecule is protected, for example as in the present invention by trehalose, the protein will denature. The significance of these hydrogen bonds to the tertiary structure is, of course, variable and the behavior of different proteins under the same conditions is not predictable.

While other proteins have been freeze-dried in the presence of trehalose, applicant is unaware of any instance wherein Factor VIII has been successfully freeze-dried in the presence of trehalose prior to the present invention.

In general, it is desirable to avoid freeze-drying due, not only to expense, but also because formation of ice crystals may distort the three-dimensional shape of the protein and itself effect denaturation. As noted in Roser I and Roser II, the virtue of trehalose is said to be that the inherent problems with freeze-drying can be avoided. As stated on page 48 of Roser I,

> Freeze-drying of pharmaceuticals is an expensive art. Although many attempts have been made to provide a firm scientific foundation for defining freeze-drying protocols, they have yet to accomplish this aim. ... The new approach is simple to use and could potentially bring great savings to biopharmaceutical product processing.

Roser I provides and teaches a method to use trehalose for carrying out dessication at high ambient temperatures, not freeze-drying with trehalose. Similarly, Roser II is specifically directed to drying at ambient temperature and atmospheric pressure in the presence of trehalose. Roser II, as does Roser I, specifically teaches away from combining freeze-drying with the use of trehalose as a cryopreservative; rather the advantage of trehalose is said to be its ability to protect proteins from denaturation during drying under ambient conditions.

The invention, however, combines the use of trehalose with the putatively less advantageous process of freeze-drying in order to obtain a stable preparation of Factor VIII. This combination, taught away from by the art that focuses on the use of trehalose *per se*, is thus not suggested by the state of the art at the time the invention was made.

The Rejection of Claims 14-19 Under 35 U.S.C. § 103

Claims 14-19 were rejected as obvious over Curtis, *et al.* (U.S. patent 5,576,291) in view of Livesey, *et al.* (U.S. patent 5,364,756). Reconsideration in light of the following is respectfully requested.

As a preliminary matter, applicant acknowledges that most of the claims as presented, in particular, claims 14, 16, 20 and 22, cover the activated form of Factor VIII described by Curtis. The distinction from Curtis in combination with Livesey does not reside in an assertion that the activated protein of Curtis is not covered by the present claims. Applicant appreciates the Examiner pointing this out in the response to argument in the Office action to which this responds.

The Examiner is correct that Curtis discloses the preparation of albumin-free recombinant Factor VIII in Example 1. The Examiner is correct that Curtis differs from the claims at least in that there is no specific direction in Curtis to freeze-dry the resulting recombinant Factor VIII in the presence of trehalose. The Examiner goes on to point out that in a general way, trehalose is listed among other possible stabilizers and the possibility of lyophilization is mentioned. Applicant agrees with the Examiner's apparent conclusion that this general disclosure is insufficient to suggest effectively that albumin-free recombinant Factor VIII be subjected specifically to freeze-drying from an aqueous solution in the presence of trehalose. The rejection, correctly therefore, does not rely solely on Curtis, *et al.,* since, as the Office recognizes, any possible suggestion to carry out the process claimed is insufficient.

Therefore, the Office combines the teachings of Curtis with those of Livesey which lists Factor VIII as among those proteins that could be preserved by Livesey's method of freeze-drying. Further, according to the Office, the freeze-drying can be conducted in a solution containing trehalose in the absence of albumin citing claim 9. The Office considers that Livesey differs from claim 7 (sic, 14-19?) in not disclosing a single embodiment having all of the claim limitations.

This is not the only manner in which Livesey differs from the invention as claimed in claims 14-16. Livesey does not suggest freeze-drying an "aqueous solution" of Factor VIII in the presence of trehalose and in the absence of albumin as required by these claims. Rather, as noted in claim 9 of Livesey itself, the solutions referred to are "vitrification solutions." These "vitrification solutions" themselves are not freeze-dried by Livesey; rather, Livesey requires that microdroplets containing a cryoprotectant and the biological material of interest be subjected to freeze-drying. Thus, for example, Livesey states at column 4, beginning at line 16, that cooling is achieved by nebulizing the solution to form discrete droplets <200 μ in diameter. These droplets are then frozen and dried "by use of a conventional freeze-dryer or a molecular distillation dryer" (lines 28-29). Thus, what is being freeze-dried by Livesey is not an aqueous solution *per se*, but rather microdroplets of a cryopreparation.

Further, it is not clear that the "vitrification solution" of claim 9 is necessarily that employed to form the microdroplets. The only instance in which this is the case is in Example 4; in Example 1, for example, the freeze-drying subsequent to nebulization is carried out in the absence of trehalose and the "vitrification solution" is only used to reconstitute the freeze-dried mammalian cells.

Thus, it cannot be said that Livesey actually suggests freeze-drying an aqueous solution of Factor VIII in the presence of trehalose and the absence of albumin. Instead, what Livesey suggests is cryopreservation of cells by nebulizing solutions of various cryoprotectants prior to freeze-drying or molecular distillation.

With respect to Example 5 mentioned by the Office, the viral vaccine is, of course, not just protein but nucleic acid containing a proteinaceous coat; in any event, it is not an aqueous solution that is freeze-dried in this example, but rather microdroplets containing the virus.

Indeed, no freeze-drying even occurred in Example 5; rather a molecular distillation dryer was used.

Thus, as the Office recognizes, neither Curtis nor Livesey taken alone suggests the invention as claimed; neither do these documents suggest the claimed invention when taken together. It does not appear that the Office action explains why the combination would suggest the claimed invention – *i.e.*, which features of Curtis would be combined with which features of Livesey to produce a suggestion that an aqueous solution of Factor VIII, free of albumin and containing trehalose, should be freeze-dried in order to stabilize Factor VIII protein. The focus of the Curtis reference is simply the use of activated Factor VIII rather than un-activated Factor VIII as a drug; there is nothing in this document relating to stabilizing procedures other than a generic discussion of how stabilization might be conducted – a discussion that falls far short of a suggestion of the method as claimed. The defect identified by the Office - that there is no particular embodiment of the claimed invention method - is not remedied by Livesey which suggests a very different approach to freeze-drying altogether (nebulizing to form microdroplets)and certainly makes no suggestion that Factor VIII be subjected to any particular process for stabilization. Indeed, the exemplified biological material in Livesey consists of cells and viruses. Taken together, even if the documents are combined, the invention is not suggested.

Further, although the rejection is based on a combination of Curtis with Livesey, no motivation for combining the teachings of these documents is provided. When a rejection is based on a combination of documents, a rationale for combination is a requisite for an appropriate rejection. This was enunciated, for example, in *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998), where the point was made that without such rationale, a rejection based on a

combination of documents must fail. No rationale at all appears to be present in the rejection as formulated.

Finally, applicant points out that an important feature of the invention as claimed is the use of trehalose as a cryoprotectant. The only documents of record that suggest that trehalose, as opposed to other cryoprotectants, is desirable, are Roser I and Roser II, which teach away from using trehalose in a freeze-drying protocol. As pointed out in these documents, the purpose of using trehalose is to avoid the disadvantages of freeze-drying. Thus, in general, the art at the time the invention was made taught away from the process claimed.

Accordingly, applicant believes that the rejection over Curtis in combination with Livesey may properly be withdrawn.

It remains only to add that the additional limitation of the inclusion of histidine included in new claims 20-22 is not suggested by either of these references.

Double-Patenting

Claims 14-19 were provisionally rejected as statutory double-patenting over claims 7 and 24-28 of copending application 08/875,796. This provisional rejection may be withdrawn since claims 7 and 24-28 are no longer present in the copending application. The invention claimed herein is not the same invention as that in allowed claims 29, 32 and 35 which require specified levels of salt and a stabilizer "consisting essentially of" trehalose. A terminal disclaimer with respect to this application is, however, enclosed. This may also answer the question raised by the Office as to pursuing what appear to be duplicate claims; this is not the case in the present application as amended.

CONCLUSION

The claims are directed specifically to a process wherein Factor VIII is stabilized by freeze-drying an aqueous solution of Factor VIII in the presence of trehalose and the absence of albumin. Trehalose as a cryoprotectant is suggested as an alternative to freeze-drying in Roser I and Roser II. Thus, the art taken as a whole at the time of the invention would not suggest use of trehalose as a cryoprotectant in a freeze-drying procedure for Factor VIII. The combination of Curtis and Livesey cited by the Office, even when made, fails to suggest the process as claimed because neither document, as recognized by the Office, suggests the specific process claimed and the combination of these documents does not result in such a suggestion. Further, no motivation to combine these documents has been provided.

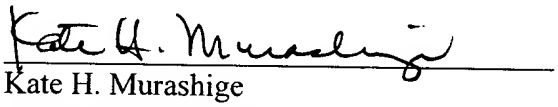
A terminal disclaimer has been submitted with respect to any double-patenting issue which, in light of the nature of the present claims and those in the parent case would be of an "obviousness-type" nature as opposed to the "same" invention.

Therefore, it is believed that claims 14-16 and 20-22 are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 559662800101.

Respectfully submitted,

Dated: December 8, 2003

By: 

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